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## **Severe neonatal hypertrophic obstructive cardiomyopathy**

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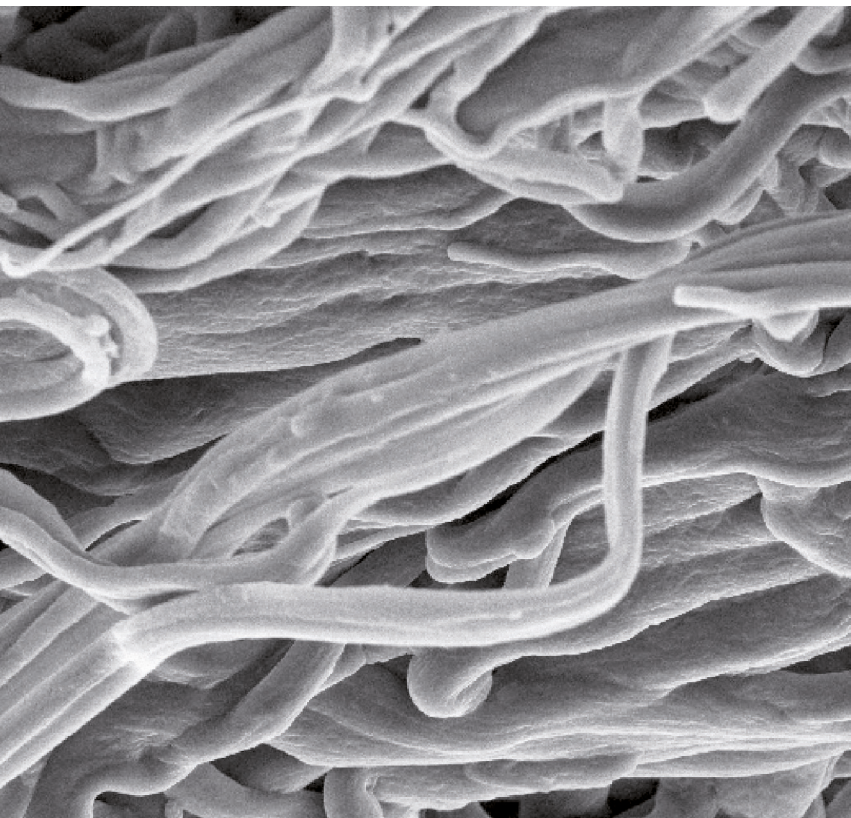
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SWISS SOCIETY OF NEONATOLOGY

# Severe neonatal hypertrophic obstructive cardiomyopathy

March 2013





This female infant was born to a 32-year-old G4/P2 at 39 weeks of gestation with an unremarkable family history. In the 19th week of gestation, the mother was hospitalized because of placenta praevia with vaginal bleeding. Thereafter, pregnancy continued uneventfully with no evidence of maternal diabetes. An ultrasound examination performed at 30 weeks of gestation was normal without structural cardiac anomaly or function. Near term, a pelvic MRI was performed because of fetal macrosomia (estimated weight of 4050 g) and previous cesarean section. MRI results were unremarkable and the infant was subsequently born by spontaneous vaginal delivery. Apgar scores were 4, 9 and 9 at 1, 5 and 10 minutes, respectively. Arterial umbilical cord pH was 7.16. The birth weight was 3750 g (P75-90), the length 50 cm (P25-50) and the head circumference 34.5 cm (P25-50).

Immediately after birth, a hyperdynamic precordium as well as a 2/6 systolic ejection murmur radiating to the axilla were noted. Brachial and inguinal pulses were well palpable, and pre- and postductal oxygen saturations were equal at 97%. The baby appeared otherwise well. Echocardiography was performed at the age of 12 hours and revealed severe hypertrophic obstructive cardiomyopathy, as well as severe valvular and supra-valvular aortic and pulmonary stenoses.

The baby, although asymptomatic at the time, was immediately transferred to the Cardiac Centre of the

Children's Hospital of Zurich for further investigations. Echocardiography confirmed the diagnosis. Within the first few days of life, the baby developed heart failure and cardiac surgery was performed on the 6th day of life. Commisurotomy of the aortic valve, transannular patch of the right ventricular outflow tract and two-patch extension of the left ventricular outflow tract were performed. The baby did not recover after cardiac surgery and required urgent reoperation: the aortic valve was replaced with a Contegra® graft with reimplantation of the coronary arteries. Weaning from cardiopulmonary bypass was not possible due to severe myocardial dysfunction and ECMO therapy was initiated. Twenty-four hours later, the entire myocardium was completely akinetic and lacked electrical activity. ECMO treatment was withdrawn and the baby died on the 8th day of life.

The unexpected diagnosis of hypertrophic cardiomyopathy with stenosis of both semilunar valves prompted genetic testing and revealed a reduced copy number on 7q11.23 in the Williams-Beuren region. The deletion was smaller than usual, but the critical genes *ELN* and *LIMK1* were affected, thus the diagnosis of Williams-Beuren syndrome was confirmed.

Autopsy revealed marked hypertrophy of the left, right and septal myocardium (Fig. 1, 2) with multiple areas of acute and subacute patchy necrosis. The coronary arteries showed severe vessel wall hyperplasia (Fig. 3).

In an aortic biopsy that had been obtained intraoperatively, there was increased medial thickness with focally fragmented lamellar architecture (Fig. 4). This vessel pathology is typical of Williams-Beuren syndrome.

*Macroscopic appearance of the heart: generalized hypertrophy of the myocardium.*



**Fig. 1**

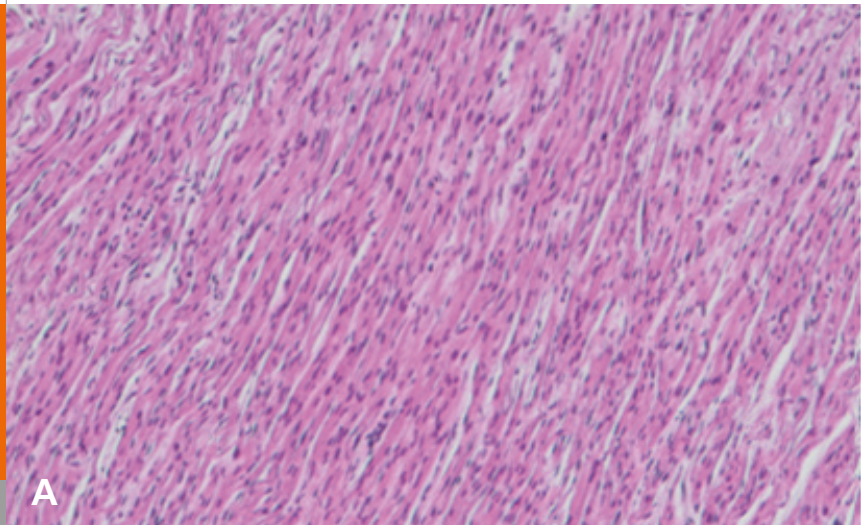
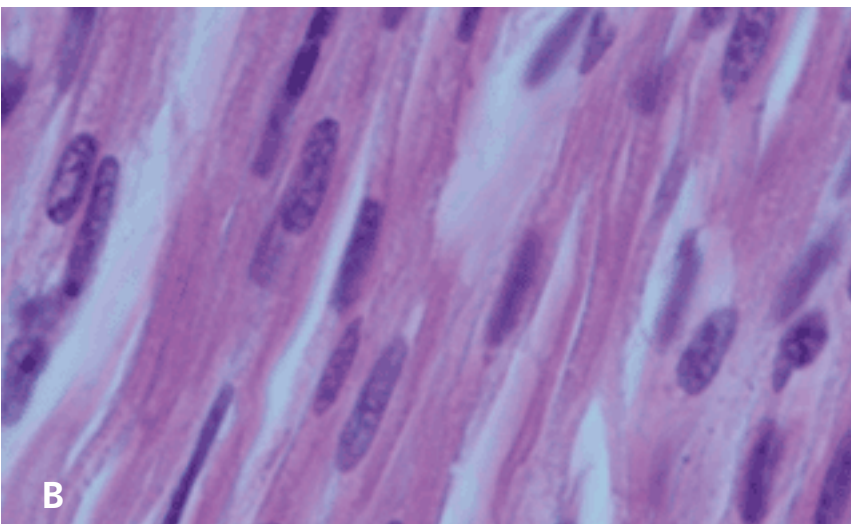


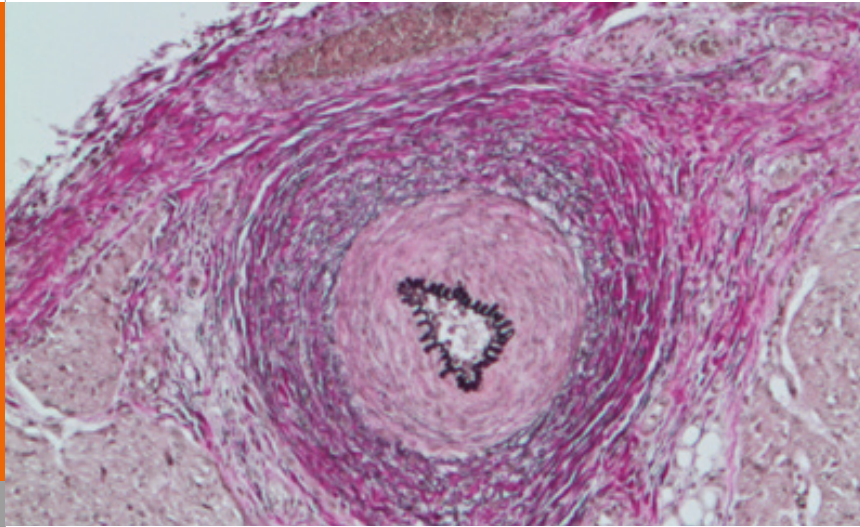
Fig. 2

A

*Septal myocardium with some hypertrophic cells and centralized nuclei (A: overview, B: detail).*

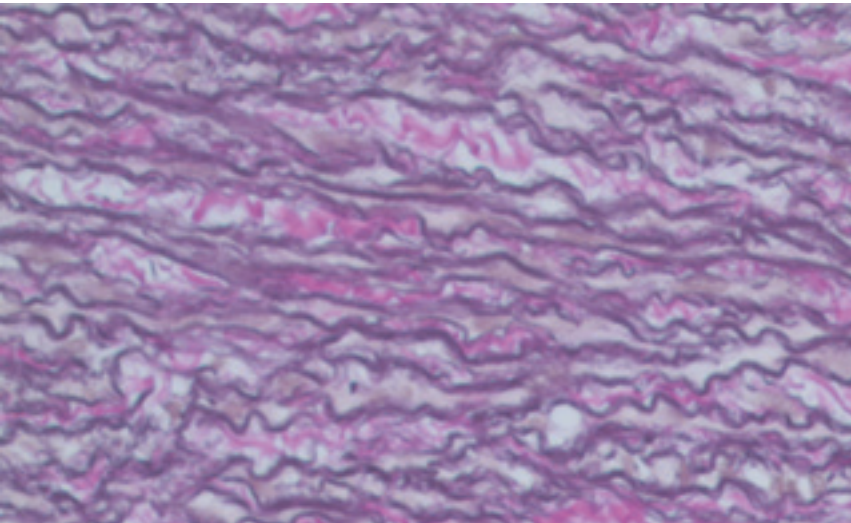






**Fig. 3**

*Hypertrophic muscular media of a coronary artery.*



**Fig. 4**

*Hypertrophic media of the aorta (not shown) with relatively well preserved lamellar architecture.*

## DISCUSSION

There are several distinct forms of cardiomyopathy: dilatative, hypertrophic, restrictive, and specific forms. In hypertrophic cardiomyopathy, the ventricular mass is increased due to structural abnormalities of the myocardium. Hypertrophy frequently involves the interventricular septum. When this leads to outflow tract obstruction, either of the right, the left, or of both ventricles, the disease entity is called obstructive cardiomyopathy. Studies among children estimate the prevalence of hypertrophic cardiomyopathy to be 3-5 cases per 1 million live births (1).

Clinical presentation varies widely. Newborn infants can be asymptomatic for some time, then present with poor feeding, excessive or unexpected weight gain, poor peripheral perfusion, oliguria, marbled skin, cold sweats, edema, tachycardia, hepatomegaly, respiratory distress as well as gallop rhythm which are the classical clinical signs of heart failure (2). Sudden cardiac death can also occur.

Differential diagnosis includes glycogen storage disease (Pompe's disease), mitochondrial disorders, several genetic disorders like Noonan syndrome or Beckwith-Wiedemann syndrome, and hypertrophic obstructive cardiomyopathy seen in infants of diabetic mothers. The latter is the most common diagnosis, and also the only one with a favorable outcome. The overall mortality of hypertrophic cardiomyopathy is approximately 1% per year. The highest mortality

is documented in infants diagnosed with hypertrophic cardiomyopathy before the age of one year (1).

Williams-Beuren Syndrome is a rare multisystem disorder described independently by Williams et al. in 1961 and Beuren et al. in 1962. The incidence ranges between 1 in 20'000 to 50'000 live births (4). In 90-95% of patients, the syndrome is caused by a deletion on the long arm of chromosome 7 which includes the elastin gene (1).

The clinical features of Williams-Beuren syndrome are highly variable. The classical phenotype includes a cute face with flat nasal bridge, short upturned nose, long philtrum, full cheeks, full lips, wide mouth and small jaw. In newborns, the dysmorphic signs may be subtle or even missing. The typical facial features are usually recognizable around four months of age (1). Almost every organ system can be affected, leading to a variety of problems (e.g., hyperacusis, recurrent otitis media, dental malocclusion and hypodontia, early onset of puberty, osteopenia, colic, abnormal weight gain, gastroesophageal reflux, constipation, bladder diverticula, nephrocalcinosis, joint laxity, joint contractures, strabismus, reduced stereopsis, soft skin, premature graying of hair, inguinal and other hernias). Neurological symptoms include mental retardation (mean IQ 55) and personality disorders. However, children with Williams-Beuren syndrome often have a friendly disposition.

Cardiovascular abnormalities are diagnosed in about 75-80% of patients. Apart from hypertrophic obstructive cardiomyopathy, the typical cardiac defect of supravalvular aortic stenosis is seen in around 70% of patients (5). Pulmonary artery stenosis, aortic hypoplasia, aortic coarctation, mitral valve prolapse and septal defects have also been described (3). In all cases, there is increased intima and media thickness of the carotid artery, accompanied by generalized elastin arteriopathy (4).

The major cause of mortality in patients with Williams-Beuren syndrome is related to the cardiovascular anomalies. Once the syndrome has been diagnosed, regular cardiac follow-up is mandatory. Because of mental retardation, only a few adults with Williams-Beuren Syndrome can live independently or have full-time employment. Most require ongoing supervision at home and in their workplace (5).

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